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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,691	09/30/2003	Veneta Hanson	0028/71160/JPW/BJA	8146

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EXAMINER	
GRUN, JAMES LESLIE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,691	HANSON ET AL.	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/08/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application clearly fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the sequences disclosed, e.g., on page 19. Applicant's attention is directed to these regulations, published at 1114 OG 29, 15 May 1990 and at 55 FR 18230, 01 May 1990.

Applicants are required to provide a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, which includes each of the sequences disclosed in the specification as required by 37 CFR 1.821(c). A substitute copy of the "Sequence Listing" in computer readable form must be provided as required by 37 CFR 1.821(e). Applicants must direct the entry of "SEQ ID NO:" identifiers for every appearance of sequences in the description or claims of the patent application. Applicants must also provide a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

The disclosure is objected to because of the following informalities: the brief description of drawings 1, and all reference to said drawings in the specification must indicate the panel of the Figure which is described or to which the reader is being referred, e.g. the Figures should be described and cited as Figure 1A or 1B; page 15, line 26, --Active-- is misspelled. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Absent further written description and guidance from applicant, one would not know or be able to predict what other "agents" or immunogenic fragments of enolase specifically bind to the relevant autoantibodies and predictably function in the assay and kit to detect the relevant autoantibodies other than intact enolase, particularly intact neuron-specific or gamma enolase.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics when coupled with a known or disclosed structure/function correlation, methods of making the claimed product, or any

combination thereof. The specification does not provide sufficient recitation of distinguishing identifying characteristics of the genus of "agents" or fragments that specifically bind the relevant autoantibodies other than for intact enolase (see e.g. page 15). As applicant provides no description or guidance for what structure(s)/fragment(s) is(are) necessary and sufficient for function of the instant intact unmodified protein(s) itself, the specification does not describe usable fragments of the protein.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of agents or fragments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement that defines a genus of molecules by only their functional activity does not provide an adequate written description of the genus. The court indicated that although applicants are not required to disclose every species

encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). However, in view of the guidance in the instant specification only to specific full-length enolase proteins which function as agents for autoantibody binding as intended by applicant, the amount of experimentation required to determine functional structures or modifications for other usable agents would also be undue. A polypeptide having 434 amino acid residues, as does SEQ ID NO: 21, has a potentially large number of antibody-binding epitopes therein and applicant provides no guidance to which epitope(s) is(are) relevant for the function of the protein. It is notoriously old and well known in the art that even single amino acid changes to a peptide epitope can have significant effects upon the binding of antibodies thereto. Even "conservative" substitutions with regard to protein structure or biochemistry may have unknown, unpredictable, and significant effects on the immunoreactivity of such a modified protein compared to the unmodified protein, particularly when the relevant epitope(s) is(are) unknown and this(these) epitope(s) has(have) the potential for being unpredictably functionally altered by **any** substitution. Relevant epitopes may be conformationally defined, not linear, and mere fragmentation may also have unknown and unpredictable effects on antibody binding. Not knowing, absent further experimentation, which modifications or fragments function and which do not leads to one having no predictability or expectation of success for the function of any given modification or fragment. Such random experimentation to identify at a later time what structure or fragment is or is not functional

and embraced by applicant's claims is undue experimentation. As applicant provides no description or guidance for what structure(s)/fragment(s) is(are) necessary and sufficient for function of the instant intact unmodified protein(s) itself when, as set forth above, even a single change of an encoded amino acid can unpredictably affect structure and function, the specification does not enable fragments of the protein. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (18 USPQ 2d 1027 (CAFC 1991)).

Therefore, only the disclosed specific full-length enolase proteins that bind to the relevant autoantibodies, but not the full breadth of the claims, meet the written description and enablement provisions of 35 U.S.C. §112, first paragraph.

Claims 1-8 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicant's specification and the prior art, such as the references of Hanson et al. (1992) and Gitlits et al. (1997), suggest that autoantibodies specific for enolase are found in samples obtained from a variety of patients. Moreover, detection of the autoantibodies in a patient with Parkinson's disease or Alzheimer's disease or glaucomatous

optic neuropathy, as is known in the art (see e.g. Horvat et al. or Maruyama et al.), would not indicate neuropsychiatric systemic lupus erythematosus in that patient. Thus, absent further written description and guidance from applicant, one would not be assured of the ability to assess neuropsychiatric systemic lupus erythematosus in patients based merely upon detection of the presence of autoantibodies in a sample from a patient not known or suspected of having systemic lupus erythematosus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 and 19-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and claims dependent thereupon, "the" likelihood, subject, or presence lack antecedent basis. The term "likely" in these claims is a relative term which renders the claims indefinite. The term "likely" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In claim 8, "the amount" lacks antecedent basis.

Claim 9 improperly depends from itself. Recitations of "the" components lack antecedent basis in this claim. It is believed that claim --8-- was intended.

In claim 10 and claims dependent thereupon, "the" likelihood, sample, subject, or presence lack antecedent basis. The term "likely" in these claims is a relative term which

renders the claims indefinite. The term "likely" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In claims 14 and 15, "the amount" lacks antecedent basis.

In claim 19 and claims dependent thereupon, the interrelationships of the components are not clear because the agent is both bound and labeled.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-21 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hanson et al. (J. Exp. Med. 176: 565, 1992) in light of the instant disclosure.

Hanson et al. detected autoantibodies in the sera of patients with systemic lupus erythematosus and central nervous system involvement that bound an antigen of approximately 50 kDa, inherently gamma enolase in light of the instant disclosure, in bovine brain, human brain, and rat neuroblastoma cell fractions. Binding was detected in Western blots or in immunofluorescent assays with labeled anti-human immunoglobulin antibodies. Controls were also assessed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Maruyama et al. (Tohoku J. Exp. Med. 197: 125, July 2002) teach detection of serum autoantibody against neuron-specific enolase in glaucoma patients.

Horvat et al. (Jugosl. Med. Biokem. 16: 217, 1997) teach detection of serum autoantibody against neuron-specific enolase in Alzheimer's and Parkinson's disease patients.

McAleese et al. (Eur. J. Biochem. 178 : 413, 1988) teach the sequence of human neuron-specific enolase compared to other enolase sequences.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James L. Grun, Ph.D.
June 14, 2006

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